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On-line TOC Monitoring in GMP Parts Washers

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Introduction

TOC (total organic carbon) analysis is one of the most common analytical methods used for cleaning validation in the pharmaceutical industry. This nonspecific method is typically used to detect the presence of organic residues on cleaned product contact surfaces. In conventional automated cleaning systems such as COP (clean out-of-place) parts washers, a sample of the final rinse water is analyzed for TOC off-line. This approach requires that a sample be manually taken from the washer and transferred to a laboratory for TOC analysis. A new technology is now available that allows this analysis to be performed by the washer itself.

With the recent regulatory developments in the pharmaceutical industry driven by ICH guidelines Q8, Q9, and Q10, and the new FDA process validation guidance document released in January 2011, the emphasis on continued process verification has increased. This poster describes a TOC monitoring system integrated into a COP parts washer. This system can provide increased productivity, meet PAT and QbD goals and provide ongoing assurance over the life cycle of the process.

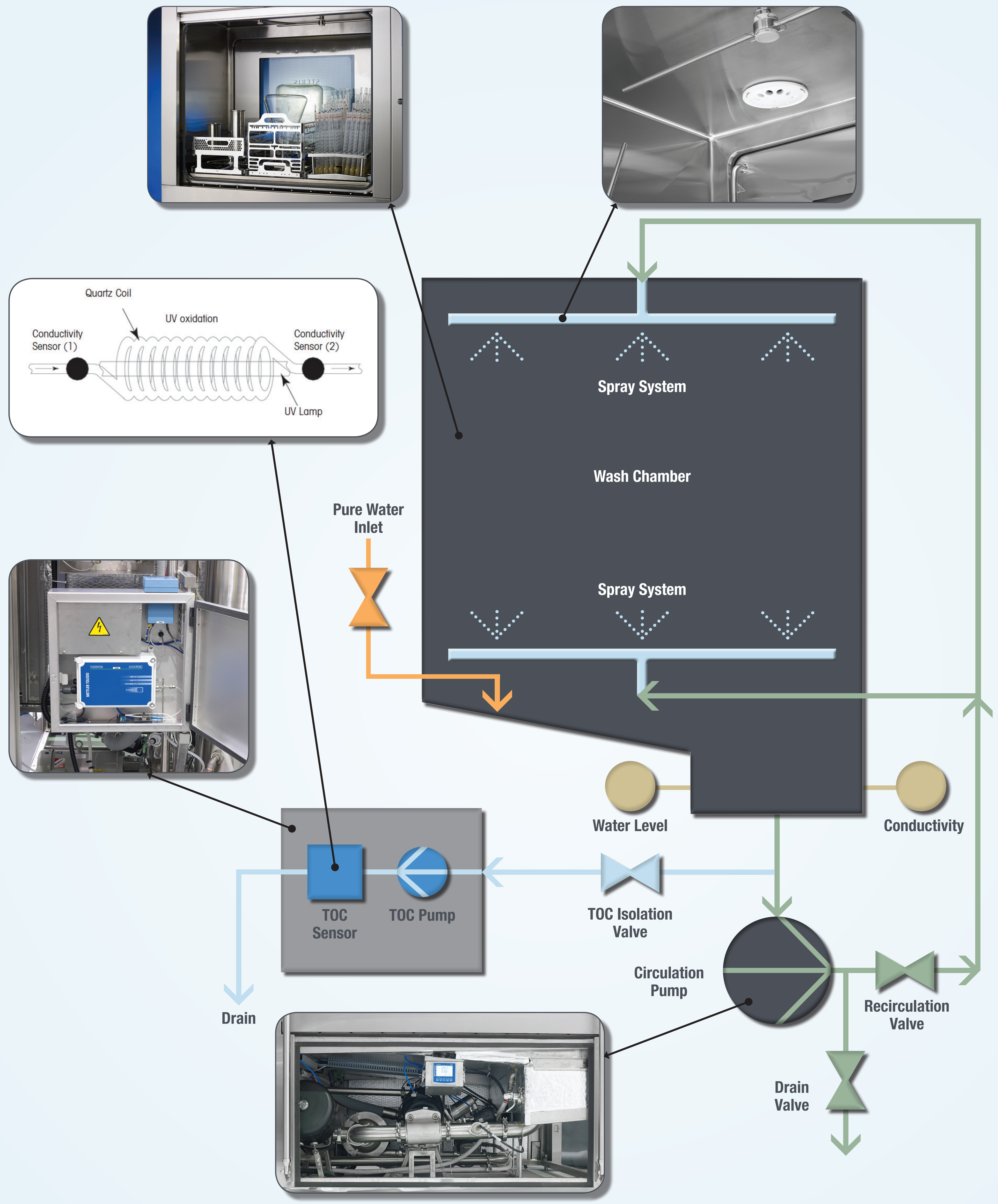
System Description

Monitoring system:

- Thornton 5000TOCe TOC sensor that is interfaced with a 770MAX Multi-Parameter Analyzer/Transmitter.
- Conductivity probe, located in the sump of the washer, that is interfaced with a Thornton M300 Conductivity Analyzer.
- Both analyzers are connected to the washer's Programmable Logic Controller (PLC).

Operation:

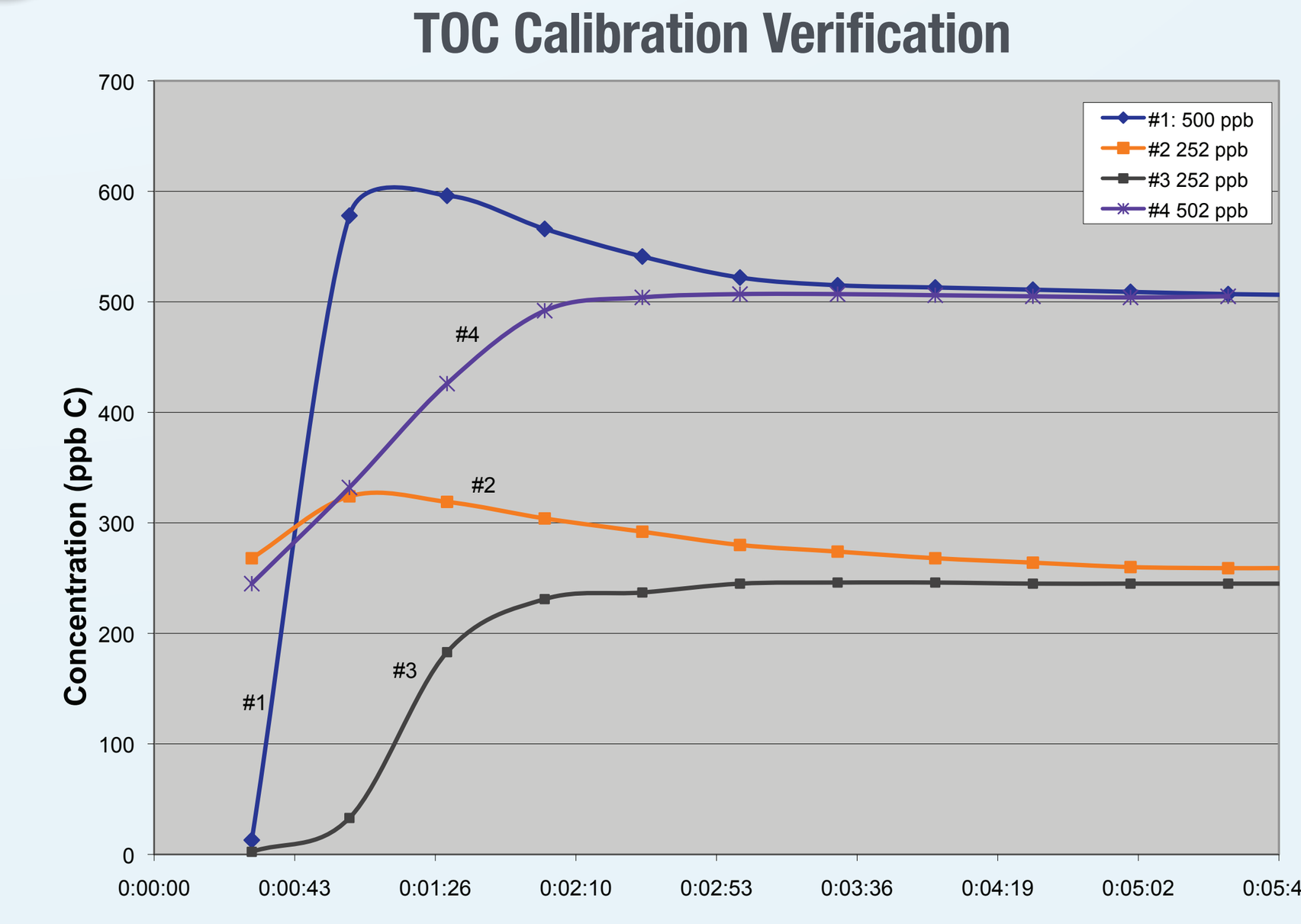
- A controlled amount of final rinse water is directed to the TOC sensor assembly through an isolation valve.
- The 5000TOCe sensor uses ultraviolet oxidation with differential conductivity as the method to determine TOC concentrations in the final rinse water sample.
- Built-in conductivity sensors provide continuous conductivity measurement before and after sample oxidation.
- The measured TOC value is then transmitted to the washer PLC, which will generate an alarm if the value is higher than the set point.



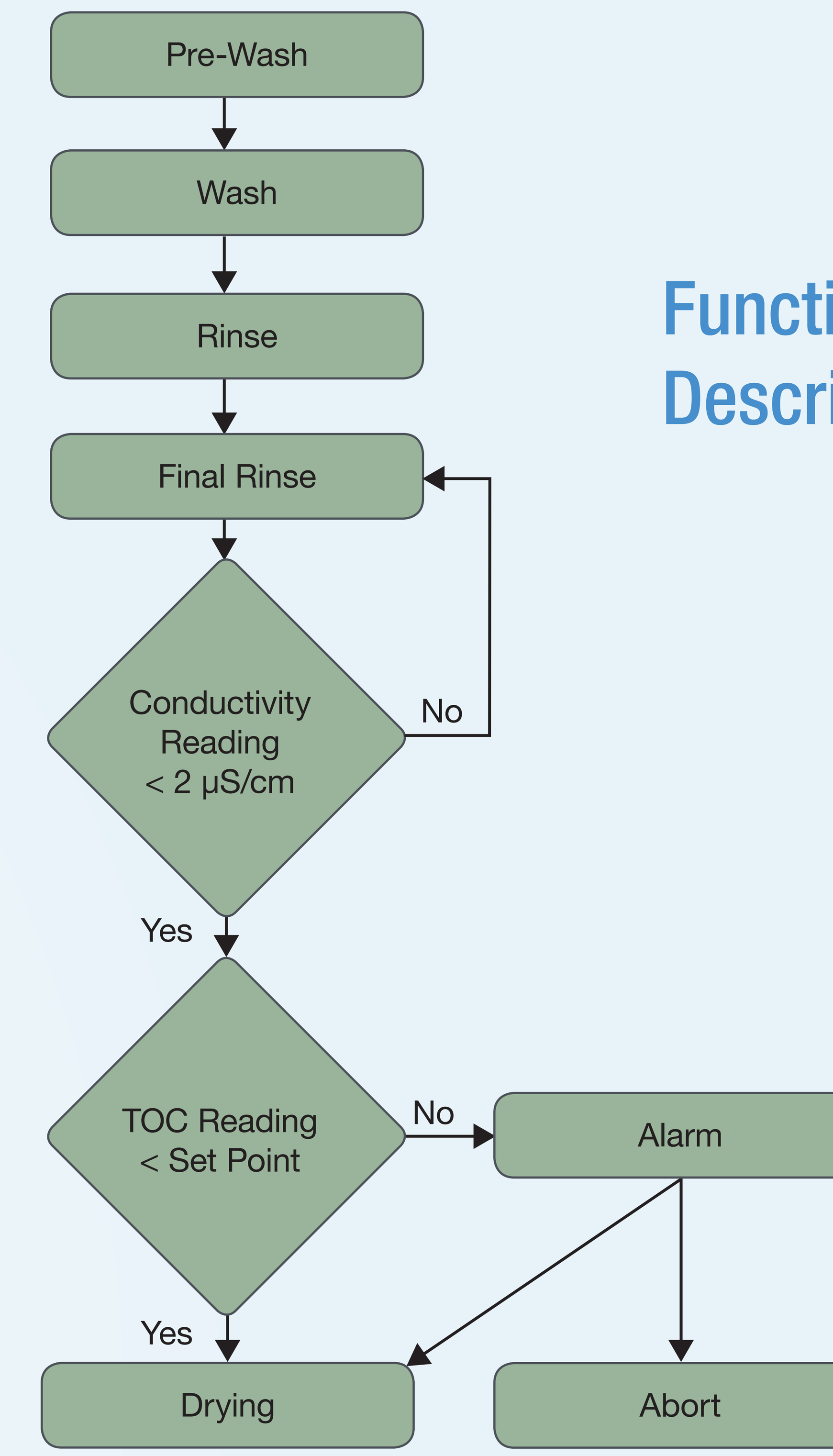
Benefits of On-line TOC

- Gives quick analytical results with reduced labor
- Reduces risk of contaminating rinse water samples
- Reduces equipment downtime
- Allows cycle time optimization
- Allows minimizing of rinse water consumption
- Allows process trending and analysis, ensures robustness
- Measures a critical quality attribute (CQA)

TOC Calibration Verification



Functional Description



Technical Data

- Sampling sequence: 6 to 12 minutes
- TOC measurement range: 1-1000 ppbC (µgC/L)
- Sensor limit of detection (LOD): 0.025 ppbC.
- Typical result using STERIS CIP 100® cleaner at 4% concentration and CIP 200® cleaner at 2% concentration:
  - Stabilization time approximately 8 minutes
  - Values measured after 3 recirculated rinses with RO water and two single-pass rinses with WFI vary between 50 and 150 ppbC.

References

1. FDA. *Guidance for Industry PAT–A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.* Rockville, MD: US Department of Health and Human Services. September 2004.

2. Verghese G, Lopolito P. *Process Analytical Technology and Cleaning. Monitoring and Analyzing the Progress of Cleaning Drives Improvement.* Contamination Control. Fall 2007.

3. Bader K, Hyde J, Watler P, Lane A. *Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management.* Pharmaceutical Engineering. January/February 2009.